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ALAN J. GRANT, ESQ.
c/o CARELLA, BYRNE, BAIN, GILFILLAN, CECCHI
STEWART & OLSTEIN
6 BECKER FARM ROAD
ROSELAND, NJ 07068

EXAMINER	
STEADMAN, DAVID J	

ART UNIT	PAPER NUMBER
1652	

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16

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/526,193	HAYDEN ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☒ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *112,114-126,131,133,135-176 and 178-196* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *112,114-126,131,133,135-157,159,161-172,176,178 and 189-196* is/are rejected.

7)☒ Claim(s) *158,160,173-175, and 179-188* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 March 2000* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *13* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Application Status

Claims 112, 114-126, 131, 133, 135-176, and 178-196 are pending in the application.

Cancellation of claims 87-111 and addition of claims 112-194 in Paper No. 13, filed 12/03/01, is acknowledged.

Amendment to claims 112, 143, 154, 155, 161, 165, and 176, cancellation of claims 113, 127-130, 132, 134, and 177, and addition of claims 195 and 196 in Paper No. 15, filed 03/13/02, is acknowledged.

Applicants' arguments filed in Paper No. 13 have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

The examiner requests that applicants provide a copy of all pending claims in the response to this Office action.

Drawings

1. The figures remain objected to by the examiner. Correction is required. It is noted that applicants request delay of filing of formal drawings until allowance of claimed subject matter. While applicants' request is acknowledged, applicants attention is drawn to 37 CFR § 1.85 regarding corrections to drawings as follows, "objections to the drawings in a utility or plant application will not be held in abeyance, and a request to hold objections to the drawings in abeyance will not be considered a bona fide attempt to advance the application to final action (§ 1.135(c))".

Claim Objections

2. Claims 174, 175, 179-188 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend upon another multiple dependent claim. Also, claims 158, 160, 173, 179, 181, 182, 184, and 187 are objected to because the claims do not refer back in the alternative only See MPEP § 608.01(n). Accordingly, the claims have not been further treated on the merits.

3. Claims 112, 135, and 139 are objected to because of the following informalities: the term "a ABC1" in claims 112, 135, and 139 is grammatically incorrect and should be replaced with, for example, "an ABC1". Appropriate correction is required.

4. Claim 146 is objected to because of the recitation of "ApoAI, ApoAII and ApoE". Abbreviations, unless otherwise obvious and/or commonly used in the art, should not be recited in the claims without at least once reciting the entire phrase. It is suggested that applicants recite the abbreviated phrase, e.g., "Apolipoprotein (Apo)AI, ApoAII and ApoE". Appropriate correction is required.

5. Claim 165 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of previous claim 160. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim Rejections - 35 USC § 112, Second Paragraph

6. Claims 114, 162-164, 176, and 191 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. Claim 114 is indefinite as being dependent upon a cancelled claim. It is suggested that applicants correct the claim dependency so that the claim is dependent upon a pending claim.

8. Claims 162-164 are confusing and lack antecedent basis. It appears the claims should be dependent upon claim 161 and not claim 160. It is suggested that applicants clarify the meaning of the claims.

9. Claim 176 is unclear as to whether "hABC1" recited in line 2 of the claim meant to be wild-type or mutant hABC1, as a compound that modulates biological activity of a mutant hABC1 polypeptide will not necessarily modulate biological activity of wild-type hABC1 polypeptide. It is suggested that applicants clarify the meaning of the term "hABC1" as being either wild-type or mutant hABC1.

10. Claim 191 is confusing in the recitation of "no detectable expression occurs when said compound is not present". It is unclear as to how no expression of the ABC1 polypeptide occurs because the cell of claim 189 expresses human ABC1. Therefore, a baseline expression of the polypeptide is expected in the presence or absence of the compound. It is suggested that applicants clarify the meaning of the claim.

Claim Rejections - 35 USC § 112, First Paragraph

11. The written description rejection of claims 112, 114-126, 131, 133, 135-157, 159, 161-172, 176, 178, and 189-196 under 35 U.S.C. 112, first paragraph, is maintained. The rejection was fully explained in a previous Office action.

Claims 112, 117, 118, 122, 123, 131, 133, 135, 137-139, 141-144, 155, 157-161, 164, 166-171, 176, 178, and 189 and claims dependent therefrom are rejected because the claims are drawn to methods of identifying modulators of a genus of mammalian ABC1 polypeptides (claims 112, 118, 122, 123, 135, 139, 161, 166, and 169), human ABC1 polypeptides (claims 133, 138, 142, 143, 159, 165, 168, 171, 176, and 189), mouse ABC1 polypeptides (claims 131, 137, 141, 157, 164, 167, and 170), or variant ABC1 polypeptides comprising 1-5 amino acid differences relative to SEQ ID NO:1 (claims 176 and 178) and optionally using parts and fragments of HDL-cholesterol (claims 116, 117, 154, and 155) or an acceptor that accepts a transported lipid (claim 144) that have not been fully described in the specification such that one of skill in the art would recognize that applicants were in possession of the claimed invention.

Applicants argue the claims have been amended to recite mammlian ABC1 polypeptides, whose use for identifying modulators thereof are fully described in the instant specification. Applicants argue human, mouse, and WHAM chicken ABC1 polypeptide sequences are disclosed and thus, assays for modulating mouse or human ABC1 polypeptides are also described. Applicants argue that critical mutations within the disclosed sequences are also described. Applicants' argument has been fully considered but is not found persuasive to overcome the instant rejection.

It is noted that applicants' claims are not so limited to those critical mutations as disclosed at, for example, Figure 8. While applicants have further limited the claims to methods for identifying modulators of a genus of mammalian, human, mouse or variants of SEQ ID NO:1 optionally using parts and fragments of HDL-cholesterol or an acceptor that accepts a transported lipid, this recitation fails to provide a sufficient description of the claimed genus of polypeptides, parts and fragments of HDL-cholesterol or lipid acceptors as it merely describes the functional features of the genus without providing any definition of the structural features of the species within the genus. The CAFC in *UC California v. Eli Lilly*, (43 USPQ2d 1398) stated that: "In claims to genetic material, however a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA", without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus". Similarly with the claimed processes of identifying modulators of a genus of polypeptides optionally using parts and fragments of HDL-cholesterol or an acceptor that accepts a transported lipid, the functional definition of the genus does not provide any structural information commonly possessed by members of the genus that distinguish the polypeptide species within the genus from other proteins such that one can visualize or recognize the identity of the members of the genus. Given this lack of description of representative species encompassed by the genera of the claims, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and

exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention. The rejection is maintained for the reasons of record and the reasons described above.

12. The scope of enablement rejection of claims 112, 114-126, 131, 133, 135-157, 159, 161-172, 176, 178, and 189-196 under 35 U.S.C. 112, first paragraph, is maintained. The rejection was fully explained in a previous Office action.

Claims 112, 116, 117, 122, 123, 131, 133, 135, 137-139, 141-144, 154, 155, 157, 159, 161, 164-171, 176, 178, and 189 and claims dependent therefrom are rejected because the specification, while being enabling for: i) a process for identifying a compound that modulates the biological activity of the human ABC1 polypeptide of SEQ ID NO:1 by detecting a difference in lipid binding in the presence of the compound relative to binding in the absence of the compound and optionally wherein the lipid is HDL-cholesterol and optionally using a recombinant cell that has been engineered to express SEQ ID NO:1 or a recombinant cell that does not express SEQ ID NO:1 without having been engineered to do so (relevant to claims 112, 116, 117, 122, 123, 131, 133); ii) a process for identifying a compound that modulates the biological activity of the human ABC1 polypeptide of SEQ ID NO:1 by detecting a difference in ATP hydrolysis in the presence of the compound relative to hydrolysis in the absence of the compound (relevant to claims 135, 137, 138); iii) a process for identifying a compound that modulates the biological activity of the human ABC1 polypeptide of SEQ ID NO:1 by detecting a difference in ATP binding in the presence of the compound relative to binding in the absence of the compound (relevant to claims 139, 141, 142); iv) a process for identifying a compound that modulates the biological activity of the human ABC1 polypeptide of SEQ ID NO:1 in a membrane by detecting a difference in lipid transport in the presence of the compound relative to transport in the absence of the compound and optionally further comprising contacting the membrane with an HDL particle and optionally wherein the lipid is HDL-cholesterol (relevant to claims 143, 144, 154, 155, 157, and 159); v) a process for identifying a compound that modulates the biological activity of the human ABC1 polypeptide of SEQ ID NO:1 in a membrane by detecting a difference in anion transport in the presence of the compound relative to transport in the absence of the compound (relevant to claims 161, 164, 165); vi) a process for identifying

a compound that modulates the biological activity of the human ABC1 polypeptide of SEQ ID NO:1 in a membrane by detecting a difference in interleukin-1β transport in the presence of the compound relative to transport in the absence of the compound (relevant to claims 166-168); vii) a process for identifying a compound that modulates the biological activity of the human ABC1 polypeptide of SEQ ID NO:1 by detecting a difference in binding to a protein in the presence of the compound relative to protein binding in the absence of the compound (relevant to claims 169-171); viii) a process for identifying a compound that modulates the biological activity of a mutant human ABC1 polypeptide of SEQ ID NO:1 having the mutations as set forth in Figure 8 by detecting a difference in binding to a lipid, a protein, ATP, and interleukin-1 in the presence of the compound relative to binding in the absence of the compound (relevant to claims 176 and 178; and ix) a process for identifying a compound that modulates the biological activity of the human ABC1 polypeptide of SEQ ID NO:1 expressed in a cell by detecting a difference in ABC1 expression in the presence of the compound relative to expression in the absence of the compound (relevant to claim 189), does not reasonably provide enablement for: i) a process for identifying a compound that modulates the biological activity of *any* mammalian, human, or mouse ABC1 polypeptide by detecting a difference in lipid binding in the presence of the compound relative to binding in the absence of the compound and optionally wherein the lipid is *any* part of HDL-cholesterol or *any* fragment of HDL cholesterol that binds ABC1 polypeptides; ii) a process for identifying a compound that modulates the biological activity of *any* mammalian, human, or mouse ABC1 polypeptide by detecting a difference in ATP hydrolysis in the presence of the compound relative to hydrolysis in the absence of the compound (relevant to claims 135, 137, 138); iii) a process for identifying a compound that modulates the biological activity of *any* mammalian, human, or mouse ABC1 polypeptide by detecting a difference in ATP binding in the presence of the compound relative to binding in the absence of the compound (relevant to claims 139, 141, 142); iv) a process for identifying a compound that modulates the biological activity of *any* mammalian, human, or mouse ABC1 polypeptide in a membrane by detecting a difference in lipid transport in the presence of the compound relative to transport in the absence of the compound and optionally further comprising contacting the membrane with *any* acceptor that accepts a transported

lipid and optionally wherein the lipid is *any* part or fragment of HDL-cholesterol (relevant to claims 143, 144, 154, 155, 157, and 159); v) a process for identifying a compound that modulates the biological activity of *any* mammalian, human, or mouse ABC1 polypeptide in a membrane by detecting a difference in ion transport in the presence of the compound relative to transport in the absence of the compound (relevant to claims 161, 164, 165); vi) a process for identifying a compound that modulates the biological activity of *any* mammalian, human, or mouse ABC1 polypeptide in a membrane by detecting a difference in *any* interleukin-1 transport in the presence of the compound relative to transport in the absence of the compound (relevant to claims 166-168); vii) a process for identifying a compound that modulates the biological activity of *any* mammalian, human, or mouse ABC1 polypeptide by detecting a difference in binding to a protein in the presence of the compound relative to protein binding in the absence of the compound (relevant to claims 169-171); viii) a process for identifying a compound that modulates the biological activity of *any* mutant human ABC1 polypeptide of SEQ ID NO:1 with 1-5 amino acid differences by detecting a difference in binding to a lipid, a protein, ATP, and interleukin-1 in the presence of the compound relative to binding in the absence of the compound (relevant to claims 176 and 178); and ix) a process for identifying a compound that modulates the biological activity of *any* human ABC1 polypeptide expressed in a cell by detecting a difference in ABC1 expression in the presence of the compound relative to expression in the absence of the compound (relevant to claim 189).

Applicants argue the claims, in light of the specification, are drawn to methods of identifying modulators of *specific* ABC1 biological activities and that the claimed methods are *not* to be interpreted as identifying modulators of any and all ABC1 biological activities. Applicants argue original claims 87-111 have been replaced with claims 112-194 that more clearly identify the claimed subject matter. Applicants argue newly added claims 135-142 recite methods of measuring ATP binding and/or hydrolysis that are well-known in the art; newly added claims 143-160 recite use of lipid or HDL transport assays that are fully supported by the specification and compounds affecting transport would be ABC1 modulators; newly added claims 176-181 are drawn to methods using mutant ABC1 polypeptides and because sequences of ABC1 polypeptides are disclosed and such mutant forms can be readily determined and used in the

claimed assays; newly added claims 182-188 recite methods of modulating triglyceride and cholesterol levels that are well-known in the art; and newly added claims 189-194 recite assays based on cellular expression of ABC1 polypeptides that can be measured using antibody binding assays. Applicants' arguments have been fully considered but are not found persuasive to overcome the rejection.

It is noted that the disclosure provides a definition of ABC1 biological activity at page 15 of the specification as "hydrolysis or binding of ATP, transport of a compound... ...or ion across a membrane, or regulation of cholesterol or phospholipid levels". Provided this definition and in view of applicants' amendment to the claims to limit the biological activities to lipid binding, ATP hydrolysis or binding, ion transport or binding, interleukin-1 transport or binding, protein-protein binding, and ABC1 polypeptide expression, one of skill in the art would recognize applicants' intended ABC1 biological activities. However, the scope of the claimed processes remains overly broad as described above. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the number of ABC1 polypeptides, ABC1 mutants of SEQ ID NO:1, parts or fragments of HDL cholesterol, acceptors of transported lipids, and interleukin-1 polypeptides broadly recited in the claims. Applicants have provided no guidance in the specification as to methods of isolating *any* mammalian, human, or mouse ABC1 polypeptide. Furthermore, the state of the art at the time of the invention (see for example Paper No. 6 IDS reference Luciani et al. *EMBO J* 15:226-235) teaches that the physiological function of an ABC1 polypeptide is unknown. Applicants have provided no guidance as to the amino acids that are conserved and a rational and predictable scheme for mutating *any* residue(s) of the polypeptide of SEQ ID NO:1 with an expectation of obtaining a functional ABC1 polypeptide. Applicants have provided no guidance or working examples for practicing the claimed processes using *any* fragments or parts of HDL cholesterol that bind to, if any, mammalian, human, or mouse ABC1 polypeptides or methods of practicing the claimed process using *any* lipid acceptor. Applicants have provided no guidance or working examples of practicing the claimed invention using *any* interleukin and furthermore, the state of the art at the time of the invention suggested that ABC1 was not involved in interleukin-1α transport (see IDS reference Hamon et al. *Blood* 90:2911-2915, 1997, specifically page 2913, Figure 1B). Therefore, the expectation

that the claimed processes can be practiced following the guidance provided in the specification is highly unpredictable and would require undue experimentation. Thus, Applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The rejection is maintained for the reasons of record and for the reasons discussed above.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 139 and 141 are rejected under 35 U.S.C. 102(b) as being anticipated by Luciani et al. (IDS reference; EMBO J 15:226-235, 1996). Claim 139 is drawn to a process for identifying a compound that modulates the biological activity of a mammalian ABC1 polypeptide by contacting a compound with a mammalian ABC1 polypeptide and ATP and detecting a difference in ATP binding in the presence of the compound relative to hydrolysis or binding in the absence of the compound. Claim 141 limits the mammalian ABC1 polypeptide of claim 139 to mouse ABC1.

Luciani teaches the functional model for ABC transporters predicts that any interference with the ability to bind or hydrolyze ATP would impair the function of the transporter (page 232, right bottom). Luciani teaches that no physiological function has been determined for ABC1 (page 226). Luciani teaches a method of inhibiting ABC1 binding to ATP using an antibody, Ab16, that specifically reacts with an ATP binding domain of ABC1 (pages 229, 233, and 234). Luciani teaches that increasing concentration of Ab16 resulted in inhibition of ABC1 biological activity, measured as mouse macrophage engulfment of apoptotic bodies (page 231, Figure 4D). This anticipates claims 139 and 141 as written.

14. Claims 161-163 and 165 are rejected under 35 U.S.C. 102(b) as being anticipated by Becq et al. (IDS reference; *J Biol Chem* 272:2695-2699, 1997). Claim 161 is drawn to a process for identifying a compound that modulates the biological activity of a mammalian ABC1 polypeptide by contacting a compound with a membrane comprising a mammalian ABC1 polypeptide and a source of one or more anions that bind ABC1 and detecting a difference in anion transport in the presence of the compound relative to transport in the absence of the compound. Claim 162 limits the anion transport to an increase in anion transport. Claim 163 limits the one or more anions of the process of claim 161 to at least two different anions. Claim 165 limits the mammalian ABC1 to human ABC1.

Becq teaches the characterization of ABC1 as an anionic transporter and provides a method of measuring the percentage I^{125} anion efflux from Xenopus laevis oocytes recombinantly expressing human ABC1 in the presence of zero or increasing concentration of various anion transport inhibitors (page 2696 and 2697, Figure 2). Becq teaches that, using this method, I^{125} anion efflux increases in the presence of cAMP (page 2697, Figure 3). This anticipates claims 161, 162, and 165 as written.

15. Claims 161, 164, and 166-168 are rejected under 35 U.S.C. 102(b) as being anticipated by Hamon et al. (IDS reference; *Blood* 90:2911-2915, 1997). Claim 161 is described above. Claim 164 limits the mammalian ABC1 of claim 161 to mouse ABC1. Claim 166 is drawn to a process for identifying a compound that modulates the biological activity of a mammalian ABC1 polypeptide by contacting a compound with a membrane comprising a mammalian ABC1 polypeptide and interleukin-1 and detecting a difference in interleukin-1 transport in the presence of the compound relative to transport in the absence of the compound. Claims 167 and 168 limit the mammalian ABC1 to mouse or human ABC1, respectively.

Hamon teaches a method for measuring I^{125} anion efflux from mouse macrophages in the presence of zero or increasing concentration of ABC1 inhibitors (page 2912 and Figure 4, page 2914). Hamon teaches a method for measuring the relative percentage secretion of interleukin-1β from mouse macrophages (pages 2911, 2912, and 2914, Figure 3) and human monocytes (pages 2912 and 2913, Figure 2) in the presence of zero or increasing concentration of ABC1 inhibitors. Hamon teaches inhibition

of interleukin-1β secretion in the presence of ABC1-specific inhibitors (Figures 3 and 4), thereby suggesting ABC1 is involved in the secretion of interleukin-1β (abstract). This anticipates claims 161, 164, and 166-168 as written.

Claim Rejections - 35 USC § 102/103

16. Claims 135 and 137 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Luciani. Claim 135 is drawn to a process for identifying a compound that modulates the biological activity of a mammalian ABC1 polypeptide by contacting a compound with a mammalian ABC1 polypeptide and ATP and detecting a difference in ATP hydrolysis in the presence of the compound relative to hydrolysis or binding in the absence of the compound. Claim 137 limits the mammalian ABC1 polypeptide of claim 135 to mouse ABC1.

Luciani discloses the teachings as described above. Luciani does not specifically teach that Ab16 prevents ABC1 hydrolysis of ATP. However, one of ordinary skill in the art would have recognized that a compound that prevents ABC1 binding to ATP necessarily prevents ABC1 hydrolysis of ATP. This anticipates or at least renders obvious claims 135 and 137 as written.

17. Claims 136 and 140 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Becq. Claims 136 and 140 limit the difference in hydrolysis or binding, respectively, of the process of claims 135 and 139, respectively, to an increase in hydrolysis or binding.

In addition to the teachings as described above, Becq teaches an ABC transporters' activity is dependent upon their interaction with ATP at the nucleotide binding site followed by hydrolysis of ATP (page 2695). Becq does not specifically teach that cAMP increases the rate of ATP binding or hydrolysis during I^{125} anion efflux. However, one of ordinary skill in the art would have recognized that efflux of I^{125} by ABC1 requires ATP and hydrolysis and therefore, upregulation of I^{125} anion efflux by cAMP necessarily resulted from increased ABC1 ATP binding and hydrolysis. This anticipates or at least renders obvious claims 136 and 140 as written.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

18. Claims 138 and 142 are rejected under 35 U.S.C. 103(a) as being unpatentable over Luciani. Claims 138 and 142 limit the processes of claims 135 and 139 to processes for identifying a compound that modulates the biological activity of a human ABC1 polypeptide by detecting differences in ATP hydrolysis (claim 138) or binding (claim 142) in the presence of the compound relative to hydrolysis or binding in the absence of the compound.

Luciani discloses the teachings described above. Luciani does not teach practicing their method of inhibiting ABC1 binding to ATP using an antibody generated against the ATP binding domain of ABC1 in human cells.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to practice the method of Luciani as described above using human cells instead of mouse macrophages. One would have been motivated for a method to practice the method of Luciani as described above using human cells instead of mouse macrophages in order to confirm the requirement of ABC1 for engulfment of apoptotic bodies in a clinically-relevant cell type, i.e., human cells. One would have a reasonable expectation of success for practicing the method of Luciani using human cells because of the results of Luciani.

Therefore, claims 138 and 142, drawn to processes for identifying a compound that modulates the biological activity of a human ABC1 polypeptide by detecting differences in ATP hydrolysis or binding in the presence of the compound relative to hydrolysis or binding in the absence of the compound. would have been obvious to one of ordinary skill in the art.

19. Claim 164 is rejected under 35 U.S.C. 103(a) as being unpatentable over Becq. Claim 164 limits the process of claim 161 to a process using mouse ABC1.

In addition to the teachings as described above. Becq also suggests further investigation of the modulation of ABC1 transporter activity using phagocytic cells, in particular, mouse macrophages (page 2699). Becq does not specifically teach using their method as described above using mouse macrophages.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to practice the method of Becq for measuring the percentage I^{125} anion efflux using mouse macrophages. One would have been motivated to practice the method of Becq using mouse macrophages because of the suggestion of Becq as described above. One would have a reasonable expectation of success for practicing the method of Becq using mouse macrophages because of the results of Becq.

Therefore, claim 164, drawn to a process for identifying a compound that modulates the biological activity of a mammalian ABC1 polypeptide by contacting a compound with a membrane comprising a mouse ABC1 polypeptide and a source of one or more anions that bind ABC1 and detecting a difference in anion transport in the presence of the compound relative to transport in the absence of the compound would have been obvious to one of ordinary skill in the art.

20. Claim 165 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hamon et al. Claim 165 limits the process of claim 161 to human ABC1.

Hamon discloses the teachings as described above. Hamon does not teach practicing their method of measuring I^{125} anion efflux in the presence of zero or increasing concentration of ABC1 inhibitors using a human cell.

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to practice the method of Hamon for measuring I^{125} anion efflux in the presence of zero or increasing concentration of ABC1 inhibitors using a human cell instead of a mouse macrophage. One would have been motivated to use a human cell instead of a mouse macrophage in order to demonstrate

the results of Hamon of parallel inhibition of anion transport and interleukin-1β secretion by ABC1 inhibitors in a medically-relevant cell, i.e., a human cell. One would have a reasonable expectation of success to practice the method of Hamon for measuring I^{125} anion efflux in the presence of zero or increasing concentration of ABC1 inhibitors using a human cell instead of a mouse macrophage because of the results of Hamon. Therefore, claim 165, drawn to a process for identifying a compound that modulates the biological activity of a human ABC1 polypeptide, would have been obvious to one of ordinary skill in the art.

21. Claims 169-171 are rejected under 35 U.S.C. 103(a) as being unpatentable over Becq in view of Hamon. Claim 169 is drawn to a process for identifying a compound that modulates the biological activity of a mammalian ABC1 polypeptide by contacting a compound with a mammalian ABC1 polypeptide and a protein that binds said polypeptide and detecting a difference in protein binding in the presence of the compound relative to binding in the absence of the compound. Claims 170 and 171 limit the mammalian ABC1 polypeptide of claim 169 to mouse or human ABC1, respectively.

In addition to the teachings as described above, Becq teaches ABC1 anion transport activity is up-regulated by cAMP-dependent protein kinases and suggest that activation of protein kinase A (PKA) increases the activity of ABC1 (page 2698). Becq does not teach a method of identifying a compound that inhibits ABC1 binding to a cAMP-dependent protein kinase.

In addition to the teachings as described above, Hamon teaches that agents able to impair secretion of interleukin-1β are of high therapeutic impact as interleukin-1β is a mediator of inflammatory reactions (page 2911).

Also, at the time of the invention, methods of identifying inhibitors of protein kinases or specific protein-protein interactions were known to one of ordinary skill in the art.

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention for a process of identifying a compound that inhibits PKA binding and phosphorylation of ABC1. One would have been motivated for a process of identifying a compound that inhibits PKA binding and phosphorylation of ABC1 in order to identify a potential therapeutic agent that prevents or reduces

secretion of interleukin-1β. One would have a reasonable expectation of success for a process of identifying a compound that inhibits PKA binding and phosphorylation of ABC1 because of the results of Becq and the ability to perform such assays of one of ordinary skill in the art at the time of the invention. Therefore, claims 169-171, drawn to a process for identifying a compound that modulates the biological activity of a mammalian, human or mouse ABC1 polypeptide by contacting a compound with a an ABC1 polypeptide and a protein that binds said polypeptide and detecting a difference in protein binding in the presence of the compound relative to binding in the absence of the compound would have been obvious to one of ordinary skill in the art.

22. Claim 172 is rejected under 35 U.S.C. 103(a) as being unpatentable over Becq in view of Hamon as applied to claims 169-171 above and further in view of GenBank Accession Number AJ012376 (IDS reference; Database GenBank, 07 January 1999) and Blom et al. (Nucleic Acids Res 26:384-386, 1998). Claim 172 limits the interacting protein of the process of claim 169 to casein kinase.

Becq and Hamon disclose the teachings as described above.

GenBank Accession Number AJ012376 teaches the nucleic acid sequence and encoded amino acid sequence of human ABC1.

Blom teaches a database for identification of protein kinase consensus phosphorylation sites in an amino acid sequence. The database of Blom indicates that 47 casein kinase-I phosphorylation sites and 35 casein kinase-II phosphorylation sites.

Also, at the time of the invention, methods of identifying inhibitors of protein kinases or specific protein-protein interactions were known to one of ordinary skill in the art.

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention for a process of identifying a compound that inhibits casein kinase binding and phosphorylation of ABC1. One would have been motivated for a process of identifying a compound that inhibits casein kinase binding and phosphorylation of ABC1 in order to identify a potential therapeutic agent that prevents or reduces secretion of interleukin-1β. One would have a reasonable expectation of success for a process of identifying a compound that inhibits casein kinase binding and phosphorylation

of ABC1 because of the results of Becq, GenBank Accession Number AJ012376, Blom, and the ability to perform such assays of one of ordinary skill in the art at the time of the invention. Therefore, claim 172, drawn to a process for identifying a compound that modulates the biological activity of a human ABC1 polypeptide, would have been obvious to one of ordinary skill in the art.

23. Claims 189, 190, and 192-194 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hamon et al. (IDS reference; *Blood* 90:2911-2915, 1997) in view of GenBank Accession Number AJ012376. Claim 189 is drawn to a process for identifying a compound that modulates the biological activity of a human ABC1 polypeptide by contacting a compound with a cell that expresses human ABC1 polypeptide and detecting a difference in expression in the presence of the compound relative to expression in the absence of the compound. Claim 190 limits the difference in expression to an increase in expression. Claim 192 limits the cell to a recombinant cell. Claims 193 and 194 limit the cell of claim 189 to a fibroblast or macrophage, respectively.

Hamon and GenBank Accession Number AJ012376 disclose the teachings as described above. Hamon does not teach practicing their method of inhibiting interleukin-1β secretion using a compound that inhibits human ABC1 expression.

Also, at the time of the invention, one of ordinary skill in the art would have been able to construct an expression vector for expression of human ABC1 or for expression of an human ABC1 antisense nucleic acid using the nucleotide sequence of GenBank Accession Number AJ012376.

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to transfect the human monocytes of Hamon with an expression vector for expression of human ABC1 or for expression of an human ABC1 antisense nucleic acid using the nucleotide sequence of GenBank Accession Number AJ012376 and screen for clones with increased or decreased expression, respectively, of human ABC1. One would have been motivated to transfect the human monocytes of Hamon with an expression vector for expression of human ABC1 or for expression of an human ABC1 antisense nucleic acid using the nucleotide sequence of GenBank Accession Number AJ012376 and screen for clones with increased or decreased expression, respectively, of human ABC1 in order to confirm the

role of ABC1 in the transport of interleukin-1β secretion and, in the case of the antisense nucleic acid, to identify an agent that inhibited interleukin-1β secretion because, as taught by Hamon, agents able to impair interleukin-1β secretion have high therapeutic impact. One would have a reasonable expectation of success for identifying an antisense nucleic acid that inhibits human ABC1 expression because of the results of GenBank Accession Number AJ012376 and the ability of one of ordinary skill in the art to design an antisense nucleic acid. Therefore, claims 189, 190, and 192-194, drawn to a process for identifying a compound that modulates the biological activity of a human ABC1 polypeptide by contacting a compound with a cell, fibroblast, or macrophage that expresses human ABC1 polypeptide and detecting a difference in expression in the presence of the compound relative to expression in the absence of the compound, would have been obvious to one of ordinary skill in the art.

Conclusion

24. No claim is in condition for allowance. All claims are rejected.

25. Claims 112-126, 131, 133, 143-157, 159, 176, 178, 190, 195, and 196, would be allowable if rewritten to overcome the objection(s) and/or rejection(s) under 35 U.S.C. 112, first and second paragraphs, set forth in this Office action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (703) 308-3934. The Examiner can normally be reached Monday-Friday from 7:30 am to 2:00 pm and from 3:30 pm to 5:30 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (703) 308-3804. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

David J. Steadman, Ph.D.

Rebecca Prouty

REBECCA E. PROUTY
PRIMARY EXAMINER
GROUP 1800
1600